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Cytokine levels in febrile seizure patients: A systematic review and meta-analysis

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ABSTRACT

Purpose: Febrile seizures (FSs) are the most common form of childhood seizures. During infection, both pro-inflammatory and anti-inflammatory cytokines are produced. Complex interactions among immune-inflammatory process, cytokine activation, and genetic factors are involved in the pathogenesis of FSs. The association between cytokines and FSs during childhood is inconclusive due to inconsistent results reported in different studies. We performed a systematic review and meta-analysis to determine an association between cytokines and FS in children.

Methods: We searched PubMed, EMBASE, and Cochrane databases for studies published up to January 2017 using the following key words: ["cytokine" OR "interleukin" OR "tumor necrosis factor alpha" OR "interferon-gamma" OR "single nucleotide polymorphism"] AND ["febrile seizure" OR "febrile convulsion"] AND ["pediatric" OR "infant" OR "child"]. Standardized mead difference (SMD) and 95% confidence intervals (CI) were calculated using standard meta-analysis techniques.

Results: A total of 6 studies enrolling 243 children with FS and 234 controls were included in the meta-analysis. A total of 4 different inflammatory mediators were. The results indicated that CSF IL-1β level and serum IL-6 level were significantly associated with FS (CSF IL-1β: SMD, 1.064; 95% CI, 0.217–1.611; $P < 0.01$, serum IL-6 SMD, 2.654; 95% CI, 2.332–2.975; $P < 0.01$).

Conclusion: The results of this meta-analysis suggest that CSF IL-1β level and serum IL-6 level are associated with an increased risk of FSs in children. Based on these results, it is expected that a therapeutic agent for specific cytokines could be developed in the future to prevent FS.

1. Introduction

Febrile seizures (FSs) are the most common form of childhood seizures, occurring in 2–5% of children younger than 6 years of age [1]. FSs are defined by the International League Against Epilepsy as an elevated or rapidly rising fever of short duration associated with uncomplicated seizure that does not predispose to epilepsy and is not accompanied by any neurologic abnormality, no previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures in children between 6 months and 5 years of age [2].

FS can be divided into 2 categories. Simple FS is a seizure that only occurs once in 24 h, is generalized, has a duration of less than 15 min, while complex FS is a seizure recurs within 24 h, is focal, and has a duration of more than 15 min [3].

The threshold fever temperature for FS varies among individuals and by age and maturation [4]. Genetic susceptibility to inflammation may influence the threshold temperature of FSs, and 17–30% of FS patients have a family history of FSs [5].

Pro-inflammatory and anti-inflammatory cytokines regulate immune response. During infection, both pro-inflammatory and anti-inflammatory cytokines are produced [6]. IL-1β, TNF- α and IL-6 are pro-inflammatory cytokines that participate in the induction of acute-phase inflammation reactions, including fever. IL-1 receptor antagonist (IL-1RA) and IL-10 are anti-inflammatory

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cytokines and have a negative feedback effect during fever [6,7]. The balance between these two cytokine groups influences the severity of the fever. Complex interactions among immune-inflammatory process, cytokine activation, and genetic factors are involved in the pathogenesis of FSs [8]. Experimental studies demonstrate that inflammation and inflammatory mediators are the main causes and propagators of both febrile and epileptic seizures [9].

Several case-control studies have been performed to measure the concentration of cytokines in the serum or cerebrospinal fluid (CSF) of seizure patients compared with that of healthy controls without seizures [10–26]. Additionally, case-control genetic association studies have been conducted to establish a potential correlation between genetic polymorphisms and susceptibility to common diseases [27].

Meta-analyses are required to pool the existing inconsistent data. A systematic literature review of case-control studies that measured cytokine concentrations was also performed.

2. Materials and methods

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

2.1. Method for searching and identifying studies

A systematic literature search was conducted in PubMed, EMBASE, Cochrane Trial (CENTRAL) by using various synonyms for epilepsy and cytokines, such as “febrile seizure”, “febrile convulsion”, “cytokine”, “interleukin”, “tumor necrosis factor alpha”, “TNF-alpha”, “interferon-gamma”, and “single nucleotide polymorphism”, with “pediatric”, “infant”, or “child”. There were no restrictions on language, population, or publication year. The last search was performed on January 17, 2017.

We included studies of human epilepsy or FSs concerning cytokine measurement in serum and cerebrospinal fluid (CSF). Animal studies, articles that were not included studies, reviews, comments, case reports, and studies with inadequate data were excluded. All titles and abstracts were independently screened by two investigators (A and BO). Both authors independently checked the remaining articles for full-text eligibility.

2.2. Study selection and data extraction

The following inclusion criteria were applied: 1) the study was designed as a case-control study, 2) it diagnosed patients with FS/epilepsy without any other neurologic complications 3) it enrolled healthy controls, 4) it measured plasma cytokine concentrations, and 5) it provided adequate data, including genotype/allele frequency in both the case and control groups to allow calculation of the pooled odds ratio. Reviews, comments, animal studies, case reports and studies with inadequate data were excluded from the meta-analysis. Additionally, we excluded studies that used a definition of FS other than that used in our study, those that stimulated seizure by using lipopolysaccharide, and studies that did not include a healthy comparison group (i.e., the control group had epilepsy, encephalopathy or CNS disorder).

The titles and abstracts of the identified articles were checked and independently reviewed by two of the authors (A and BO), and discrepancies were resolved by discussion. The following data were extracted: the first author, publication year, study design, study location, ethnicity, study population, sample size, sample material, investigated cytokine gene, and the cytokine levels of the case and control groups. Any discrepancies in the interpretations of the data were resolved via discussion with a third reviewer.

2.3. Quality assessment

The two authors separately assessed the quality of the included studies. Any disagreement was resolved via discussion with a third reviewer, after which the study was reevaluated. We evaluated case control studies by using the Newcastle-Ottawa Scale. Nine points were given to studies of the highest quality, which were considered to have sufficiently “high quality” for inclusion in the meta-analysis. A total score ≤ 3 was considered to represent “low quality,” a score of 4 or 5 was considered to represent “moderate quality,” and a score ≥ 6 was considered to represent “high quality.”

2.4. Data synthesis and analysis

The mean differences and 95% confidence intervals (CIs) were calculated from the extracted data. We assessed interstudy heterogeneity by using I^2 statistics. The I^2 value was expressed as a percentage of the total variation across studies; when $I^2 > 50\%$, the assumption of homogeneity was deemed invalid, and the random effects model (DerSimonian-Laird method) was applied; otherwise, the fixed model (Mantel-Haenszel method) was used for the meta-analysis. A sensitivity analysis was performed by removing each study sequentially to evaluate the robustness of the combined estimates and to examine its contribution to the pooled odds ratio (OR). Publication bias was evaluated by using funnel plots, Egger’s test and the Begg-Mazumdar rank correlation test. $P < 0.05$ was considered statistically significant. The meta-analysis was performed using Comprehensive Meta-Analysis version 2.0 (Biostat, Englewood, NJ, USA).

3. Result

3.1. Literature search and selection

Fig. 1 shows how relevant studies were identified for this meta-analysis and why studies were excluded. Among a total of 206 studies that were identified from the initial search, 3 additional studies were added; 27 duplicates were then removed. After the abstracts and titles of 182 studies were reviewed, 31 articles remained. Through the full text review, 25 studies were excluded (the reasons are described in Fig. 1), and finally, 6 reports were included in this meta-analysis.

3.2. Characteristics of the included studies

A total of 6 studies were selected for this meta-analysis. All the studies were prospective case-controlled. Quality was evaluated with the Newcastle-Ottawa Scale, and all the studies were awarded 7 to 8 stars, indicating high quality (Table 1).

Overall, 243 FS patients and 234 controls were enrolled in all the included studies. The characteristics of the included studies are summarized in Table 2. A total of 4 different inflammatory mediators were investigated in these studies. The studies reported protein levels in serum or CSF and compared them with those of controls. We conducted meta-analyses of serum IL-1β levels based on five studies [10,19,23,25,28], CSF IL-1β based on two studies [10,28], serum TNF-α based on two studies [23,28] and serum IL-6 based on two studies [23,29]. The cytokine levels of patients and controls were expressed in pg/ml and significant difference was shown in P-value. Consistent significant differences in certain cytokines were not detected.

3.3. Meta-analysis of serum IL-1β levels

Serum IL-1β levels were investigated in five case-control studies with 143 patients with FS and 134 healthy controls. There